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A robust two-dimensional hydrogen-bonded network for the predictable assembly of ternary co-crystals of furosemide

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Consideration of the geometrical features of the functional groups present in furosemide has enabled synthesis of a series of ternary co-crystals with predictable structural features, containing a robust asymmetric two-dimensional network.

Co-crystals of active pharmaceutical ingredients (APIs) are currently of great interest to the pharmaceutical industry as they afford scope for tuning the physical properties of a drug and offer reproducible control over composition. It has also been suggested¹ that co-crystals may be less prone to polymorphism than the constituent API. This has implications for Intellectual Property (IP) in developing APIs into suitable solid dosage forms as polymorphism is a concern in the pharmaceutical industry. The prediction of crystal packing arrangements, based solely on the structure of molecular components, is of major interest in the search for new co-crystals of APIs and represents one of the foremost challenges in organic crystal engineering.² Current efforts in molecular crystal engineering focus on targeting and reproducing a particular supramolecular synthon.³ This approach has been extremely successful, although it affords little control over the crystal-packing characteristics of ancillary functional groups in the molecules. A further level of complexity in co-crystal formation is introduced through the inclusion of a third component. A number of strategies have successfully been applied to the design of ternary co-crystals.⁴

Here, we demonstrate how the identification of a neutral asymmetric two-dimensional hydrogen-bonded network leads to a new family of ternary crystals of the API furosemide (4-chloro-N-furfuryl-5-sulfoamylantranilic acid) in the presence of the co-crystal former 4,4′-bipyridine, through the inclusion of a third component. The ternary systems have been created following consideration of the geometry and dimensionality of the preferred hydrogen-bonding interactions of carboxylic acid, sulphonamide and pyridyl functional groups, leading to co-crystals with predictable crystal symmetry and structural features.

All of the co-crystals described were initially synthesized by a process of liquid-assisted grinding.⁵ Products were initially screened by powder X-ray diffraction to identify suitable targets. Crystallisation of the selected polycrystalline materials to yield single crystals suitable for structure solution was then carried out from solution. Details are provided in the ESI†.

Furosemide is a loop diuretic used in the treatment of oedema and arterial hypertension. The structures of three distinct crystalline forms have been determined.⁶ All contain the acid-acid supramolecular synthon but exhibit differences in the hydrogen bonding network associated with the sulphonamide groups. The commonly available Form 1 is the thermodynamically stable polymorph; the other two forms are metastable and can be converted to Form 1 by grinding.

The molecular structure of furosemide contains both a carboxylic acid and a sulphonamide functional group. The pseudo-tetrahedral-shaped sulphonamide group, in comparison to the planar carboxylic acid group, provides additional dimensionality for hydrogen bonding interactions.⁷ Both solvates and co-crystals of furosemide have been reported,⁸ significantly, including those in which the ability of the planar carboxylic acid group to form a two-dimensional acid-pyridine supramolecular heterosynthon is exploited.⁹

Furosemide (fus) readily forms a co-crystal [(fus)₃-(bipy)₉] (I) with 4,4′-bipyridyl (bipy) from a fus:bipy mixture of molar ratio 1:0.5. The structure of (I) contains an acid-pyridine supramolecular heterosynthon, with the bipyridyl molecule located at an inversion centre. The sulphonamide donors and the carboxylic acid acceptors of furosemide participate in N(2)-H(2)-·-O(1) and N(3)-H(1)-·-O(1) hydrogen bonding interactions to form a host network of furosemide molecules in which bipyridyl molecules occupy guest positions (Fig. 1).

Fig. 1. Packing arrangement in co-crystal (1) viewed along [010]. Key: carbon, black circles; nitrogen, blue circles; oxygen, red circles; sulphur, yellow circles; chlorine, green circles; hydrogen, small open circles. Light dashed lines denote hydrogen bonds.

Considering the ditopic hydrogen-bond acceptor nature of bipyridyl and the ability of the non-planar sulphonamide group of furosemide to participate in multiple hydrogen-bonding interactions, the ternary co-crystals have been designed to provide a new family of ternary co-crystals, containing an acid-acid supramolecular synthon in the presence of a third component.
interactions, we anticipated binary co-crystal formation at a 1:1 fus:bipy molar composition, through an alternating arrangement of fus and bipyrindyl molecules. However, powder X-ray diffraction data of the product of solvent drop grinding of such a mixture revealed the components remain as a physical mixture at this composition\textsuperscript{10} (see the ESI†). This provided the starting point for our investigation of three-component co-crystals containing furosemide and bipyrindyl. When a third component, such as dimethyl sulphoxide (DMSO), dimethylformamide (DMF) or methanol (MeOH), was added to the 1:1 fus-bipy mixture a series of three-component crystalline phases could be isolated, which may also be regarded as co-crystal solvates.

Crystallization from DMSO led to the isolation of single crystals of [(fus):bipy):-(DMSO)]\textsubscript{3} (2) after 3 days. Structural analysis by single crystal X-ray diffraction reveals the presence of DMSO molecules in the crystal structure. DMSO acts as a conventional hydrogen bond acceptor through the sulphoxide group which is involved in O(6)···H(7)N(1) interactions with the N-H group of the sulphonamide group of furosemide (Fig. 2). In addition, the furosemide molecules participate in hydrogen bonding with the pyridyl groups through O(1)H(1)···N(4) and N(1)H(6)···N(3) interactions. The hydrogen bonding between furosemide and the other components is in accordance with the principle of hierarchy, proposed by Etter.\textsuperscript{11} In addition, a methyl group of DMSO participates in a weak C(24)H(28)···O(4) interaction with the sulphone group of furosemide to form an asymmetric two-dimensional network as shown in Fig. 2.

![Fig. 2 Two-dimensional hydrogen-bonding network observed in co-crystal (2), viewed along [010]. Key as for Fig. 1.](image1)

Utilisation of methanol as the crystallization medium resulted in co-crystals subsequently identified as [(fus):bipy):-(MeOH)]\textsubscript{3} (3). Analogous to co-crystal (2), the carboxylic O-H and the syn (with respect to chlorine) N-H donors of furosemide are preferentially hydrogen bonded to the pyridyl nitrogen of bipyrindyl through O(1)H(1)···N(4) and N(1)H(6)···N(3) interactions (Fig. 3). These fus-bipy aggregates are linked by the third component, in this case methanol, through N(1)H(7)···O(6) and O(6)H(25)···O(3) interactions extending infinitely along the crystallographic a axis (Scheme 1). The three components assemble to form a two-dimensional network of hydrogen bonding interactions as shown in Scheme 1. Although crystallisation of the polycrystalline product arising from synthesis in the presence of DMF (4) was not successful, refined lattice parameters derived from powder diffraction data for (4) compare well with those obtained for the single-crystal study of (3), providing strong support for the presence of the same two-dimensional hydrogen-bonded network in (4).

![Scheme 1: Schematic illustration the two-dimensional network observed in all ternary co-crystals. R=furfuryl, TC=ternary component (DMF; DMSO; MeOH; ethanol; 2-propanol; 1-butanol; ethylene glycol; 1,4-butenediol; hydroquinone). The dotted lines indicate hydrogen bonding interactions.](image2)
In all of the ternary co-crystals presented here, the lattice metrics \(a\), \(c\) and the angle between them, \(\beta\), are principally determined by the dimensions of the asymmetric two-dimensional hydrogen bonded network, leading to a high degree of consistency in the measured values. In the absence of any significant hydrogen bonding/non-covalent interactions along the \(b\) axis, this lattice parameter is determined by the long axis of the fuoroamide molecule, and therefore influenced by the conformational flexibility of fuoroamide. We tested this hypothesis by investigating ternary systems in which molecules containing a single hydroxyl group are replaced with those containing dihydroxy-groups. Consideration of the structures of the ternary co-crystals (2)–(7) leads to the expectation that the three components, crystallising in the space group \(P\overline{1}\), would arrange with the two-dimensional hydrogen-bonded network extending from both ends of a difunctionalised third component. The diols ethylene glycol, 1,4-butanediol and hydroquinone were selected as ternary components. Solvent-drop grinding followed by crystallization produced three ternary co-crystals (8), (9) and (10) with the composition \([\text{fus}.]_2\cdot(\text{bipy})_2\cdot\text{diol}_n\cdot\text{H}_2\text{O}\). As anticipated, the ternary co-crystals (8), (9) and (10) crystallize in the space group \(P\overline{1}\) with retention of the asymmetric two-dimensional network and the stacking interactions between aromatic moieties of fuoroamide and bipyridyl molecules, similar to co-crystals (2) and (3) (ESI†).

In conclusion, we have demonstrated that consideration of simple geometric principles, together with careful selection of components, leads to the identification of a robust asymmetric two-dimensional hydrogen-bonded network, which serves as the prototype for a new family of co-crystals. This has enabled a targeted approach to be adopted in the selection of a ternary component leading to the predictable synthesis of new ternary co-crystals with control over symmetry, gross structural features and lattice metrics that depend on the two-dimensional network. The pseudo-tetrahedral shape of the sulphonamide group and the planarity of the carboxylic acid groups are central to all of the ternary co-crystals synthesised. The study demonstrates that networks that can maintain their dimensionality and integrity when changes occur in the ancillary functional groups, provide a degree of predictability in the crystal packing arrangements in the solid state. Identification of robust \(n\)-dimensional networks may therefore offer a means of improving the effectiveness of crystal engineering. This network serves as the blueprint for the prediction of the gross structural features in ternary co-crystals. The series of ternary co-crystal presented here also provide insights into the process of crystallization, details of which will be presented in due course.

**Notes and references**

8. (a)B.I. Harriss, L. Vella-Zarb, C. Wilson and I. Radosavljevic Evans, Cryst. Growth Des., 2014, 14, 783; (b) V.S. Minkov, A.A.

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**Table 1:** Unit cell parameters of all the ternary co-crystals presented here.

<table>
<thead>
<tr>
<th>3(^{\text{rd}}) component</th>
<th>(a/\AA)</th>
<th>(b/\AA)</th>
<th>(c/\AA)</th>
<th>(\alpha^{\circ})</th>
<th>(\beta^{\circ})</th>
<th>(\gamma^{\circ})</th>
<th>Volume ((\AA^3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO (2)</td>
<td>9.7483(4)</td>
<td>10.4805(4)</td>
<td>14.1432(5)</td>
<td>83.747(2)</td>
<td>86.117(2)</td>
<td>65.552(2)</td>
<td>1129.39(9)</td>
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<td>Methanol (3)</td>
<td>7.3552(9)</td>
<td>9.3457(11)</td>
<td>18.124(2)</td>
<td>80.525(6)</td>
<td>82.376(6)</td>
<td>75.758(6)</td>
<td>1185.52(2)</td>
</tr>
<tr>
<td>DMF (4)</td>
<td>7.4522(2)</td>
<td>9.315(5)</td>
<td>18.557(7)</td>
<td>87.16(9)</td>
<td>74.80(1)</td>
<td>76.94(4)</td>
<td>1213.95(3)</td>
</tr>
<tr>
<td>Ethanol (5)</td>
<td>7.193(8)</td>
<td>9.780(6)</td>
<td>18.694(2)</td>
<td>89.88(5)</td>
<td>75.50(3)</td>
<td>73.17(1)</td>
<td>1208.96(5)</td>
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<tr>
<td>2-Propanol (6)</td>
<td>7.860(5)</td>
<td>10.001(2)</td>
<td>18.402(4)</td>
<td>76.13(1)</td>
<td>76.56(5)</td>
<td>70.94(2)</td>
<td>1257.41(2)</td>
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<tr>
<td>1-Butanol (7)</td>
<td>7.537(4)</td>
<td>9.374(3)</td>
<td>18.282(2)</td>
<td>81.67(7)</td>
<td>80.54(5)</td>
<td>75.6(3)</td>
<td>1226.57(8)</td>
</tr>
<tr>
<td>Ethylene glycol (8)</td>
<td>6.7510(5)</td>
<td>9.5719(6)</td>
<td>18.6178(3)</td>
<td>84.977(4)</td>
<td>89.783(4)</td>
<td>73.488(4)</td>
<td>1146.76(14)</td>
</tr>
<tr>
<td>1,4-Butanediol (9)</td>
<td>7.3972(7)</td>
<td>9.3373(8)</td>
<td>18.1141(16)</td>
<td>80.504(4)</td>
<td>82.039(4)</td>
<td>75.173(4)</td>
<td>1186.81(19)</td>
</tr>
<tr>
<td>Hydroquinone (10)</td>
<td>6.9302(4)</td>
<td>9.9356(6)</td>
<td>18.6298(11)</td>
<td>83.633(3)</td>
<td>89.624(3)</td>
<td>72.794(3)</td>
<td>1217.14(3)</td>
</tr>
</tbody>
</table>


10. Solvent drop grinding of 1:1 co-crystals was performed in the presence of cyclohexane and n-heptane, which contain no conventional hydrogen bond donor and acceptor sites.


Identification of a two-dimensional hydrogen-bonded network leads to a new family of ternary co-crystals of furosemide